
1 Changes to Approved New Drug Applications or Abbreviated New Drug Applications

I. INTRODUCTION

The holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) can make postapproval changes in accordance with added Section 506A of the FDA Modernization Act. There are specific reporting requirements for postapproval changes in components and composition, manufacturing sites, manufacturing process, specifications, package labeling, miscellaneous changes, and multiple related changes. Reporting categories for changes relating to specified biotechnology and specified synthetic biological products regulated by the Center for Drug Evaluation and Research (CDER) are found in the guidance for industry entitled *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997). Information specific to products is developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances, that provide recommendations on reporting categories.

II. REPORTING CATEGORIES

Section 506A of the Act provides for four reporting categories that are distinguished in the following paragraphs.

A “major change” is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product (506A(c)(2)). A major change requires the submission of a supplement and approval by the Food and Drug Administration (FDA) before distribution of the product made using the change (506A(c)(1)). This type of supplement is called, and should be clearly labeled as, a Prior Approval Supplement. An applicant may ask the FDA to expedite its review of a Prior Approval Supplement for public health reasons (e.g., drug shortage) or if a delay in making

the change described in the supplement would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled as, a Prior Approval Supplement—Expedited Review Requested. Requests for expedited review based on extraordinary hardship should be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A “moderate change” is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to the FDA at least 30 days before the distribution of the product made using the change (506A(d)(3)(B)(i)). This type of supplement is called, and should be clearly labeled as, a Supplement—Changes Being Effectuated in 30 Days. The product made using a moderate change cannot be distributed if the FDA informs the applicant within 30 days of receipt of the supplement that a Prior Approval Supplement is required (506A(d)(3)(B)(i)). For each change, the supplement must contain information determined by the FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (506A(b)). If the FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended with the missing information. The FDA may identify certain moderate changes for which distribution can occur when the FDA receives the supplement (506A(d)(3)(B)(ii)). This type of supplement is called, and should be clearly labeled as, a Supplement—Changes Being Effectuated. If, after review, the FDA disapproves a Changes Being Effectuated in 30 Days supplement or a Changes Being Effectuated supplement, the FDA may order the manufacturer to cease distribution of the drugs that have been made using the disapproved change (506A(d)(3)(B)(iii)).

A “minor change” is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors

may relate to the safety or effectiveness of the product. The applicant must describe minor changes in its next annual report (506A(d)(1)(A) and (d)(2)).

An applicant can submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol should be submitted as a Prior Approval Supplement if not approved as part of the original application.

III. GENERAL REQUIREMENTS

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify the FDA about each change in each condition established in an approved application beyond the variations already provided for in the application (506A(a)).

An applicant making a change to an approved application under Section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21 of the Code of Federal Regulations (e.g., 21 CFR parts 210, 211, 314). For example, manufacturers must comply with relevant CGMP validation and record-keeping requirements and must ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection. A Changes Being Effected supplement for labeling changes must include 12 copies of the final printed labeling (21 CFR 314.50(e)(2)(ii)).

Except for a supplemental application providing for a change in labeling, an applicant should include a statement in a supplemental application or amendment certifying that the required field copy (21 CFR 314.50) of the supplement or amendment has been provided.

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES

A. ASSESSMENT OF THE EFFECTS OF THE CHANGE

A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the holder validates (i.e., assesses) the effects of the change on the identity, strength, quality, purity, and potency of the product as these factors may relate to the safety or effectiveness of the product (506A(b)). For each change, the supplement or annual report must contain information determined by the FDA to be appropriate and must include

the information developed by the applicant in assessing the effects of the change (506A(b), (c)(1), (d)(2)(A), and (d)(3)(A)). Recommendations on the type of information that should be included in a supplemental application or annual report are available in guidance documents. If no guidance is available on the type of information that should be submitted to support a change, the applicant is encouraged to contact the appropriate chemistry or microbiology review staff.

1. Conformance to Specifications

An assessment of the effect of a change on the identity, strength, quality, purity, or potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, or drug product affected by the change conforms to the approved specifications. A “specification” is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container closure systems and their components and in-process materials. For the purpose of defining specifications, “acceptance criteria” are numerical limits, ranges, or other criteria for the tests described. Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

2. Additional Testing

In addition to confirmation that the material affected by manufacturing changes continues to meet its specification, the applicant should perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product have been or will be affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the component directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance or drug product, and the effect of the change on the quality of the product. For example:

- Evaluation of changes in the impurity or degradation product profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests

to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level.

- Evaluation of the hardness or friability of a tablet after changes in formulation or manufacturing procedure.
- Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could include, for example, multipoint or multimedia dissolution profiling or an *in vivo* bioequivalence study.
- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system.

B. EQUIVALENCE

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, or potency of the drug product. Typically this is accomplished by comparing test results from prechange and postchange material and determining whether the test results are equivalent. Simply stated: Is the product made after the change equivalent to the product made before the change? An exception to this general approach is that when bioequivalence should be redocumented for certain ANDA postapproval changes, the comparator should be the reference-listed drug. Equivalence comparisons frequently require a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this reason, as well as for other reasons, “equivalent” does not necessarily mean “identical.” Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

C. ADVERSE EFFECT

Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these suboptimal manufacturing changes, but sometimes the applicant wishes to put them into practice. If an assessment concludes that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, the change should be filed in a Prior Approval Supplement, regardless of the recommended reporting category for the change. For example, a type of process change with a recommended filing category of a Supplement—Changes Being Effected in 30 Days could cause a new degradant to be formed that requires qualification or identification. However, the applicant’s degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. The applicant should submit this change in a Prior Approval Supplement

with appropriate information to support the continued safety and effectiveness of the product. During the review of the Prior Approval Supplement, the FDA will assess the impact of any adverse effect on the product as it may relate to the safety or effectiveness of the product.

V. COMPONENTS AND COMPOSITION

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes and should be filed in a Prior Approval Supplement, unless exempted by regulation or guidance (506A(c)(2)(A)). The deletion or reduction of an ingredient intended to affect only the color of a product may be reported in an annual report. Guidance on changes in components and composition that may be filed in a Changes Being Effected Supplement or annual report is not included in this document because of the complexity of these recommendations, but it may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

VI. MANUFACTURING SITES

A. GENERAL CONSIDERATIONS

CDER should be notified about a change to a different manufacturing site used by an applicant to manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates; package drug products; label drug products; or test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Sites include those owned by the applicant or contract sites used by an applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered to be those that perform labeling of the drug product’s primary or secondary packaging components. Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. The supplement or annual report should identify whether the proposed manufacturing site is an alternative or replacement to those provided for in the approved application.

A move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, should be filed as a Prior Approval Supplement if the site does not have a satisfactory CGMP inspection for the type of operation being moved. For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of

the product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these manufacturing site changes will be the same for all types of drug products and operations. For manufacturing sites used to manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or perform primary packaging operations, the potential for adverse effect and, consequently, the recommended reporting category depend on various factors such as the type of product and operation being performed. For this reason, recommended reporting categories may differ depending on the type of drug product and operations.

Except for those situations described in Sections VI.B.4, VI.C.1.b, and VI.D.5, moving production operations between buildings at the same manufacturing site or within a building, or having construction activities occur at a manufacturing site, do not have to be reported to CDER. A move to a different manufacturing site that involves other changes (e.g., process, equipment) should be evaluated as a multiple related change (see Section XII) to determine the appropriate reporting category.

B. MAJOR CHANGES (PRIOR APPROVAL SUPPLEMENT)

The following are examples of changes that are considered to have substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by the FDA for the type of operation that is being moved, or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than 2 years
2. A move to a different manufacturing site, except one used to manufacture or process a drug; substance intermediate, when the new manufacturing site has not had a satisfactory CGMP inspection for the type of operation being moved
3. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or when the formulation modifies the rate or extent of availability of the drug; or for (2) the manufacture or processing of in-process materials with modified-release characteristics; examples of these types of drug

products include modified-release solid oral dosage forms, transdermal systems, liposomal products, depot products, oral and nasal metered-dose inhalers, dry powder inhalers, and nasal spray pumps

4. Transfer of manufacturing of an aseptically processed sterile drug substance or aseptically processed sterile drug product to a newly constructed or refurbished aseptic processing facility or area or to an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved products; for example, transferring the manufacture of a lyophilized product to an existing aseptic process area where no approved lyophilized products are manufactured or where the approved lyophilized products being manufactured have dissimilar container types or sizes to the product being transferred
5. Transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site: Once this change has been approved, subsequent site changes to the facility for similar product types and processes may be filed as a Supplement—Changes Being Effectuated in 30 Days

C. MODERATE CHANGES (SUPPLEMENT—CHANGES BEING EFFECTED)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a Prior Approval Supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see Sections VI.B.1 and 2).

1. Supplement—Changes Being Effectuated in 30 Days

- a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance
- b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site, except as provided for in Section VI.B.4

- c. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and of (2) modified-release solid oral dosage-form products
- d. A move to a different manufacturing site for testing whether (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing

2. Supplement—Changes Being Effected

- a. A move to a different manufacturing site for the manufacture or processing of the final intermediate

D. MINOR CHANGES (ANNUAL REPORT)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a Prior Approval Supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see Sections VI.B.1 and 2).

1. A move to a different manufacturing site for secondary packaging
2. A move to a different manufacturing site for labeling
3. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates, other than the final intermediate
4. A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application, and the facility has a satisfactory CGMP inspection for the type of operation being performed
5. A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site
6. A move to a different manufacturing site for the ink imprinting of solid oral dosage-form products

VII. MANUFACTURING PROCESS

A. GENERAL CONSIDERATIONS

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product. In some cases there may be a substantial potential for adverse effect, regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change should be filed in a Prior Approval Supplement.

B. MAJOR CHANGES (PRIOR APPROVAL SUPPLEMENT)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Changes that may affect the controlled (or modified) release, metering, or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form
2. Changes that may affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components, including
 - Changes in the sterilization method (e.g., gas, dry heat, irradiation); these include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa
 - Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation
 - Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity-displacement steam process with a process using superheated water spray)
 - Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel vs. glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line
 - Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling; Once this change has been approved, subsequent

process changes for similar product types in the same barrier system or isolator may be filed as a Supplement—Changes Being Effected in 30 Days

Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time

Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa

Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50% beyond the validated limits in the approved application

Changes in sterilizer load configurations that are outside the range of previously validated loads

Changes in materials or pore-size rating of filters used in aseptic processing

3. The following changes for a natural product:

Changes in the virus or adventitious agent removal or inactivation methods; this is applicable to any material for which such procedures are necessary, including drug substance, drug product, reagents, and excipients

For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line

For drug substance and drug product, establishment of a new master cell bank or seed

4. Any fundamental change in the manufacturing process or technology from that currently used by the applicant, for example:

a. Drug product

Dry to wet granulation, or vice versa

Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave)

b. Drug substance

Filtration to centrifugation, or vice versa

Change in the route of synthesis of a drug substance

5. The following changes for drug substance:

Any process change made after the final intermediate processing step in drug substance manufacture

Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile or the physical, chemical, or biological properties

6. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage-form drug product when

the ink as changed is not currently used on CDER-approved products

7. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification

C. MODERATE CHANGES (SUPPLEMENT—CHANGES BEING EFFECTED)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effected in 30 Days

a. For drug products, any change in the process, process parameters, or equipment, except as otherwise provided for in this guidance

b. For drug substances, any change in process or process parameters, except as otherwise provided for in this guidance

c. For natural protein drug substances and drug products:

Any change in the process, process parameters, or equipment, except as otherwise provided for in this guidance

An increase or decrease in production scale during finishing steps that involves new or different equipment

Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters

d. For sterile products, drug substances, and components, as appropriate:

Changes in dry heat depyrogenation processes for glass container systems for products that are produced by terminal sterilization processes or aseptic processing

Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume but not filter materials or pore size rating) that require additional validation studies for the new parameters

Filtration process changes that provide for a change from single to dual product sterilizing filters in series, or for repeated filtration of a bulk

Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that results in changes to validated operating parameters (time, temperature, F_0 , and others)

Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by more than 50% beyond the validated limits in the approved application when bioburden limits are unchanged

- e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material

2. Supplement—Changes Being Effected

- a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports to or is represented to possess
- b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized product

D. MINOR CHANGES (ANNUAL REPORT)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

- 1. For drug products and protein drug substances, changes to equipment of the same design and operating principle or changes in scale, except as otherwise provided for in this guidance (e.g., Section VII.C.1.c; see FDA guidance for industry on the *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* [November 1994])
- 2. A minor change in an existing code imprint for a dosage form; for example, changing from a numeric to alphanumeric code
- 3. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage-form drug product when the ink is currently used on CDER-approved products
- 4. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage-form drug product other than a modified-release dosage form
- 5. A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions)
- 6. Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by no more than 50% beyond the validated limits in the approved application when bioburden limits are unchanged

VIII. SPECIFICATIONS

A. GENERAL CONSIDERATIONS

All changes in specifications from those in the approved application must be submitted in a Prior Approval Supplement unless otherwise exempted by regulation or guidance (506A(c)(2)(A)).

Specifications (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container and closure systems and in-process materials. For the purpose of defining specifications, acceptance criteria are numerical limits, ranges, or other criteria for the tests described. Examples of a test, an analytical procedure, and acceptance criteria are an assay, a specific fully described high-pressure liquid chromatography procedure, and 98.0%–102.0%. The recommendations in this section also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions. A regulatory analytical procedure is the analytical procedure used to evaluate a defined characteristic of the drug substance or drug product. The analytical procedures in the U.S. Pharmacopeia/National Formulary (USP/NF) are those legally recognized under section 501(b) of the Act as the regulatory analytical procedures for compendial items. The applicant may include in its application alternative analytical procedures to the approved regulatory procedure for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, the regulatory analytical procedure is used. In Sections B–D below, the use of the term “analytical procedure” without a qualifier such as “regulatory” or “alternative” refers to analytical procedures used to test materials other than the drug substance or drug product.

B. MAJOR CHANGES (PRIOR APPROVAL SUPPLEMENT)

The following are examples of changes in specifications that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

- 1. Relaxing an acceptance criterion, except as otherwise provided for in this guidance (e.g., Section VIII.C.1.b)
- 2. Deleting any part of a specification, except as otherwise provided for in this guidance (e.g., Section VIII.D.2)
- 3. Establishing a new regulatory analytical procedure
- 4. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality,

purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application

5. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as otherwise noted; for example, a change from a high-pressure liquid chromatography procedure that distinguishes impurities to one that does not, to another type of analytical procedure (e.g., titrimetric) that does not, or to one that distinguishes impurities but for which the limit of detection or limit of quantitation is higher
6. Relating to testing of raw materials for viruses or adventitious agents: (1) relaxing an acceptance criteria, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application

C. MODERATE CHANGES (SUPPLEMENT—CHANGES BEING EFFECTED)

The following are examples of changes in specifications that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effected in 30 Days

- a. Any change in a regulatory analytical procedure other than editorial or those identified as major changes
- b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials before the final intermediate, starting materials introduced before the final drug substance intermediate, or drug substance intermediates (excluding final intermediate), except as provided for in Section VIII.B.6
- c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials before the intermediate, starting materials introduced before the final drug substance intermediate, or drug substance

intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as provided for in Section VIII.B.6

- d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions; for example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and aseptic filling

2. Supplement—Changes Being Effected

- a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports to or is represented to possess; for example, adding a new test and associated analytical procedure and acceptance criterion
- b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application

D. MINOR CHANGES (ANNUAL REPORT)

The following are examples of changes in specifications that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Any change in a specification made to comply with an official compendium
2. For drug substance and drug product, the addition, deletion, or revision of an alternative analytical procedure that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application
3. Tightening of acceptance criteria
4. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced before

the final drug substance intermediate, in-process materials before the final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application

IX. PACKAGE

A. GENERAL CONSIDERATIONS

The potential for adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct product testing for conformance with the approved specification.

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

B. MAJOR CHANGES (PRIOR APPROVAL SUPPLEMENT)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved product of the same dosage form and same route of administration; for example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for use with an ophthalmic ointment
2. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change to an ink or adhesive

used on the permeable or semipermeable packaging component to one that has never been used in a CDER-approved product of the same dosage form, same route of administration, and same type of permeable or semipermeable packaging component (e.g., low-density polyethylene, polyvinyl chloride)

3. A change in the primary packaging components for any product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler)
4. For sterile products, any other change that may affect product sterility assurance such as
 - A change from a glass ampule to a glass vial with an elastomeric closure
 - A change to a flexible container system (bag) from another container system
 - A change to a prefilled syringe dosage form from another container system
 - A change from a single-unit-dose container to a multiple-dose container system
 - Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels)
 - Changes in the size or shape of a container for a sterile drug product
5. Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases)
6. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system

C. MODERATE CHANGES (SUPPLEMENT—CHANGES BEING EFFECTED)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effectuated in 30 Days

- a. A change to or in a container closure system, except as otherwise provided for in this guidance
- b. Changes in the size or shape of a container for a sterile drug substance

2. Supplement—Changes Being Effectuated

- a. A change in the size or shape of a container for a nonsterile drug product, except for solid dosage forms (see Section IX.D.2 regarding solid dosage forms)
- b. A change in or addition or deletion of a desiccant

D. MINOR CHANGES (ANNUAL REPORT)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium
2. A change in the size or shape of a container containing the same number of dose units, for a nonsterile solid dosage form
3. The following changes in the container closure system of solid oral dosage-form products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage-form products:

Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap

Changing from one plastic container to another of the same type of plastic (e.g., high-density polyethylene container to another high-density polyethylene container)

Changes in packaging materials used to control odor (e.g., charcoal packets)

Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon)

Increasing the wall thickness of the container

A change in or addition of a cap liner

A change in or addition of a seal (e.g., heat induction seal)

A change in an antioxidant, colorant, stabilizer, or mold-releasing agent for production of the container or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage-form products

A change to a new container closure system when the container closure system is already

approved in the NDA or ANDA for other strengths of the product

4. The following changes in the container closure system of nonsterile liquid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical products):

Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap

Increasing the wall thickness of the container

A change in or addition of a cap liner

A change in or addition of a seal (e.g., heat induction seal)

5. A change in the container closure system of unit-dose packaging (e.g., blister packs) for nonsterile solid dosage form-products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved products of the same type (e.g., solid oral dosage form, rectal suppository)
 6. The following changes in the container closure system of nonsterile semisolid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid products:
- Changes in the closure or cap
- Increasing the wall thickness of the container
- A change in or addition of a cap liner
- A change in or addition of a seal
- A change in the crimp sealant
7. A change in the flip seal cap color, as long as the cap color is consistent with any established color-coding system for that class of drug products

X. LABELING

A. GENERAL CONSIDERATIONS

A drug product labeling change includes changes in the package insert, package labeling, or container label. An applicant should promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations.

All labeling changes for ANDA products must be consistent with section 505(j) of the Act.

B. MAJOR CHANGES (PRIOR APPROVAL SUPPLEMENT)

Any proposed change in the labeling, except those that are designated as moderate or minor changes by regulation or guidance, should be submitted as a Prior Approval Supplement. The following list contains some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data
4. Changes based on data from preclinical studies
5. Revision (expansion or contraction) of population based on data
6. Claims of superiority to another product
7. Change in the labeled storage conditions, unless exempted by regulation or guidance

C. MODERATE CHANGES (SUPPLEMENT—CHANGES BEING EFFECTED)

A Changes Being Effectuated Supplement should be submitted for any labeling change that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdose; adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product; deletes false, misleading, or unsupported indications for use or claims for effectiveness; or is specifically requested by the FDA. The submission should include 12 copies of final printed labeling. The following list includes some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event because of information reported to the applicant or agency
2. Addition of a precaution arising out of a post-marketing study
3. Clarification of the administration statement to ensure proper administration of the product
4. Labeling changes, normally classified as major changes, that the FDA specifically requests be implemented using a Changes Being Effectuated Supplement

D. MINOR CHANGES (ANNUAL REPORT)

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report. The following list includes some examples that are currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201) without a change in the content of the labeling
2. Editorial changes, such as adding a distributor's name
3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included
4. Labeling changes made to comply with an official compendium

XI. MISCELLANEOUS CHANGES

A. MAJOR CHANGES (PRIOR APPROVAL SUPPLEMENT)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug to the drug as manufactured without the change or to a reference-listed drug (506A(c)(2)(B))
2. Addition of a stability protocol or comparability protocol
3. Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2)
4. An extension of an expiration dating period based on data obtained under a new or revised stability testing protocol that has not been approved in the application or on full shelf-life data on pilot-scale batches using an approved protocol

B. MODERATE CHANGES (SUPPLEMENT—CHANGES BEING EFFECTED)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product

as these factors may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effectuated in 30 Days

- a. Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product; extension of an expiration date that has previously been reduced under this provision should be filed in a Supplement—Changes Being Effectuated in 30 Days even if it is based on data obtained under a protocol approved in the application

2. Supplement—Changes Being Effectuated

- a. No changes have been identified.

C. MINOR CHANGES (ANNUAL REPORT)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. An extension of an expiration dating period based on full shelf-life data on full production batches obtained under a protocol approved in the application
2. Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period
3. A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances
4. Non-USP reference standards:
 - Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application
 - Tightening of acceptance criteria for existing reference standards to provide greater assurance of product purity and potency

XII. MULTIPLE RELATED CHANGES

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes, or a components and composition change may necessitate a change in a specification. For multiple related changes for which the recommended reporting categories for the

individual changes differ, CDER recommends that the filing be in accordance with the most restrictive of those reporting categories recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the filing be in accordance with the reporting category for the individual changes. For the purposes of determining the reporting category for moves between buildings, the terms “different manufacturing site” and “same manufacturing site” are defined as follows. Same manufacturing site: The new and old buildings are included under the same drug establishment registration number, and the same FDA district office is responsible for inspecting the operations in both the new and old buildings. Different manufacturing site: The new and old buildings have different drug establishment registration numbers, or different FDA district offices are responsible for inspecting operations in the new and old building.

The change to a different manufacturing site should be filed in a Prior Approval Supplement when the new manufacturing site has never been inspected by the FDA for the type of operation being moved, the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than 2 years, or the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.

Examples of postapproval manufacturing site changes and filing consequences include:

- An applicant wants to move the manufacture of an immediate-release tablet to a different manufacturing site that currently manufactures, and has satisfactory CGMP status for, capsules and powders for oral solution. This manufacturing site change should be filed in a Prior Approval Supplement because the new manufacturing site does not have a satisfactory CGMP inspection for immediate-release tablets.
- An applicant wants to contract out his or her packaging operations for immediate-release tablets and capsules and modified-release capsules. The potential contract packager has a satisfactory CGMP status for immediate-release and modified-release capsules but has never packaged immediate-release tablets. The packaging site change for the immediate-release tablet products should be filed in a Prior Approval Supplement. The packaging site change for the capsule products should be filed as recommended in section VI of this guidance for packaging sites with a satisfactory CGMP inspection.
- An applicant wishes to consolidate his or her product testing to a single analytical laboratory at a manufacturing site. This manufacturing site

produces various solid oral dosage-form products, has an operational analytical laboratory currently at the site, and has satisfactory CGMP inspections for the manufacturing occurring at the facility. Some of the products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories are not inspected on a dosage form/type of drug substance-specific basis. The satisfactory CGMP inspection of the analytical laboratory, which was performed as part of the CGMP inspection for manufacture of the solid oral dosage form products, is considered to apply to all dosage forms, including those not actually produced at the site.

Different reporting categories are proposed for changes to or the addition of certain components based on whether the component/material has been used in and has been in contact with CDER-approved products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a product approval because similar subsequent changes then have a reduced potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. For example, certain changes in the container closure systems of solid oral dosage form products may be included in the annual report, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage-form products (see Section IX.D.3). If the primary packaging component material has not been used in or has not been in contact with CDER-approved solid oral dosage-form products, then submission of the change in an annual report is not recommended. CDER-approved products are considered those subject to an approved NDA or ANDA. When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved product.

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, the applicant has the option of filing the change for a single NDA or ANDA, using the higher recommended reporting category and, after approval, filing similar subsequent changes for other NDAs and ANDAs, using the lower recommended reporting category.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other criteria for the tests described

Active Ingredient/Drug Substance—Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient, including those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3)

Component—Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3))

Container Closure System—The sum of packaging components that together contain and protect the dosage form; this includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product

Drug Product—A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient, generally, but not necessarily, in association with inactive ingredients (21 CFR 210.3(b)(4))

Final Intermediate—The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance must involve covalent bond formation or breakage; ionic bond formation (i.e., making the salt of a compound) does not qualify. As a consequence, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate

Inactive Ingredients—Any intended component of the drug product other than an active ingredient

In-Process Material—Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)). For drug substance, in-process materials are considered those materials that are undergoing change (e.g., molecular, physical)

Intermediate—A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes a drug substance

Package—The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap)

Packaging Component—Any single part of a container closure system

Primary Packaging Component—A packaging component that is or may be in direct contact with the dosage form

Reference-Listed Drug—The listed drug identified by the FDA as the drug product on which an applicant relies

in seeking approval of its abbreviated application (21 CFR 314.3)

Satisfactory CGMP Inspection—A satisfactory CGMP inspection is an FDA inspection during which no objectionable conditions or practices were found during (No Action Indicated), or an inspection during which objectionable conditions were found, but corrective action is left to the firm to take voluntarily, and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated). Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP reports information on the CGMP compliance status of firms that manufacture, package, assemble, repack, relabel, or test human drugs, devices, biologics, and veterinary drugs. All FOI requests must be in writing and should follow the instructions found

in the reference entitled *A Handbook for Requesting Information and Records from FDA*. An electronic version of this reference is available on the Internet at <http://www.fda.gov/opacom/backgrounders/foiahand.html>.

Secondary Packaging Component—A packaging component that is not and will not be in direct contact with the dosage form

Specifications—The quality standards (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems and in-process materials

Validate the Effects of the Change—To assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug